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AG a container comprising an aqueous solution wherein the aqueous solution comprises at least one surfactant and liquid-filled liposomes; and

a means for introducing a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm into the aqueous solution.

#### Remarks

This is a preliminary amendment to the above-mentioned U.S. non-provisional application filed August 16, 2001.

Claims 1-71 are pending.

The marked-up version of the specification is found in Appendix I, attached to this preliminary amendment, and titled "Marked-Up Version of Page 2, Paragraph 3, Line 16". The amendment is shown by text stricken through to indicate deletions and underlined text to indicate insertions.

The marked-up version of amended claims is found in Appendix II, attached to this preliminary amendment, and titled "Marked-Up Version of Rewritten Claims". The amendments are shown by text stricken through to indicate deletions and underlined text to indicate insertions.

The specification is amended at page 2, paragraph 3, line 16, to correct an obvious typographical error. Basis for the amendment is found throughout the specification, for example, on page 3, line 10. Accordingly, no new matter is added.

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Claims 46, 51, 55, 59, and 63 are amended to cancel the multiple dependency of the claims. Support for the amendment is found throughout the application. Accordingly, no new matter is added. Applicants retain the right to pursue any cancelled subject matter during prosecution of the present application or in any continuation or divisional application.

Summary

Applicants submit that this application is in condition for allowance. A favorable action passing this case to issue is therefore respectfully requested. If a telephone interview would be of assistance in advancing prosecution of this application, Applicants' agent invites the Examiner to contact him at the number provided below.

Respectfully submitted,



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Peter L. Dolan, Ph.D.  
Agent for Applicants  
REGISTRATION NO.46,307

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Appendix IMarked-Up Version of Page 2, Paragraph 3, Line 16

Liquid and solid contrast agents containing entrapped gas are well known in the art. See, e.g., U.S. Patent No. 4,235,871; U.S. Patent No. 4,265,251; U.S. Patent No. 4,442,843; U.S. Patent No. 4,533,254; U.S. Patent No. 4,572,203; U.S. Patent No. 4,657,756; U.S. Patent No. 4,681,199; U.S. Patent No. 5,088,499; U.S. Patent No. 5,147,631; U.S. Patent No. 5,228,446; U.S. Patent No. 5,271,928; U.S. Patent No. 5,380,519; U.S. Patent No. 5,413,774; U.S. Patent No. 5,527,521; U.S. Patent No. 5,531,980; U.S. Patent No. 5,547,656; U.S. Patent No. 5,558,094; U.S. Patent No. 5,573,751; U.S. Patent No. 5,585,112; U.S. Patent No. 5,620,689; U.S. Patent No. 5,715,824; U.S. Patent No. 5,769,080; EP 0 122 624; EP 0 727 225; WO 96/40285; and WO 99/65467. The microbubbles provided by these contrast agents act as sound wave reflectors due to the acoustic differences between the gas microbubble and surrounding liquid.

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Appendix IIMarked-Up Version of Rewritten Claims

46. (Amended) A method of ultrasound imaging in a patient in need of such ultrasound imaging comprising:

administering to the patient an effective amount of a formulation of ~~any one of claims 1-45~~;

allowing a sufficient period of time for the circulation of the gas microsphere composite to reach the targeted area; and

performing ultrasound imaging on the patient.

51. (Amended) A method of treating heart disease, inflammation, infection, cancer or thromboembolic disease in a patient in need of such treatment comprising:

administering to the patient an effective amount of a formulation of ~~any one of claims 1-45~~, wherein one or more of the liquid-filled liposomes independently comprises a therapeutic agent;

allowing a sufficient period of time for the circulation of the gas microsphere composite to the targeted area; and

applying ultrasound energy to the region of pathology in the patient sufficient to cause the therapeutic agent to be released from the microsphere liposome composite at the region of pathology.

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55. (Amended) A method for preparing a formulation of ~~any one of~~ claims 1-45 comprising:

contacting a suspension of liposomes in a aqueous solution comprising at least one lipid or one surfactant; and  
mixing the suspension with a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm sufficient to provide the formulation.

59. (Amended) A method for preparing a formulation of ~~any one of~~ claims 1-45 comprising:

contacting a suspension of liposomes in a aqueous solution comprising at least one therapeutic agent and at least one surfactant; and  
mixing the aqueous liposome suspension with a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm sufficient to provide the formulation.

63. (Amended) A kit for the preparation of a formulation of ~~any one of~~ claims 1-45 comprising:

a container comprising an aqueous solution wherein the aqueous solution comprises at least one surfactant and liquid-filled liposomes; and

a means for introducing a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm into the aqueous solution.